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Genomic tracing of the elusive liver cancer ancestor

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COMMENTARY ON:

Progenitor-derived hepatocellular carcinoma model in the rat. Andersen JB, Loi R, Perra A, Factor VM, Ledda-Columbano GM, Columbano A, Thorgeirsson SS. Hepatology. 2010 Apr;51(4): 1401–9.

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The cancer stem cell (CSC) hypothesis has sturdily re-emerged in the last decade. Advocates of this model estimate that a significant number (if not all) of human cancers are developed and sustained by a reduced number of cells with "stemness" properties such as self-renewal, unlimited proliferative capacity, and asymmetric division. Theoretically, tumor cells are organized according to these properties, with CSCs located at the top of this hierarchical pyramid [1]. There is also strong debate regarding the origin of CSCs, existing data implicates de-differentiation, arrest, and/or trans-differentiation in their generation. Robust evidence supports the CSC model in some hematological malignancies, whereas data in solid tumors are yet inconclusive.

Hepatocellular carcinoma (HCC) is an increasing health problem in United States and Europe, mainly due to the augmentation of hepatitis C virus infection [2]. In fact, mortality has doubled during the 1990–2005 interval in the USA [3]. Unlike most solid tumors, it usually arises on a previously damaged organ. Liver cirrhosis of different etiologies (e.g., viral hepatitis, alcohol consumption, NASH) is the precursor to HCC in more than 80% of patients. In this context, inflammation and hepatocyte proliferation/regeneration are the pathological substrates that trigger hepatocarcinogenesis, although additional factors such as certain viral proteins (e.g., HCV core, HBX protein) may also contribute to this process. Experimental data demonstrate activation and proliferation of progenitor cells in cirrhotic livers, but their precise oncogenic role remains controversial. In addition, cirrhosis favors the development of dysplastic foci and nodules (i.e., preneoplastic lesions for HCC onset [4]), although, little is known about the molecular changes and cellular compartments (e.g., progenitor cells, mature hepatocytes, cholangiocytes, etc.) implicated in the cirrhosis-dysplasia-HCC transition.

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A recent study by Andersen et al. provides new insights into the role of progenitor cells in HCC development, upon genomic analysis of liver nodules in a rat model that recapitulates different stages of human hepatocarcinogenesis [5]. The animal model entails two chemical carcinogens and a partial hepatectomy that expand adult stem cells and induce tumors, histologically resembling HCC. Rats were euthanized at different time points (2.5, 9, and 14 months) and the resulting hepatic nodules (i.e., focal lesions, adenomas, early and advanced HCC) were classified according to their staining status for glutathione S-transferase (i.e., a marker lost as stem cells differentiate toward hepatocytes) and CK19 (i.e., a hepatic progenitor cell marker present also in adult biliary epithelium). In addition, nodules were microdissected and profiled using whole-genome expression microarrays. Authors found a direct correlation between CK19 staining and progressive stages of liver oncogenesis in this model, being universal in HCC. Inverse correlation between CK19 staining and markers of hepatocyte differentiation (e.g., HNF4) suggested that CK19+ lesions could retain a progenitor cell origin. Interestingly, unsupervised clustering of gene expression data identified two different groups of hepatic nodules, clusters R1 and R2, which mimicked CK19 staining status. Subsequent supervised analysis found dominance of AP-1 signaling and enrichment of the stem cell module map in CK19+ nodules, reinforcing their progenitor origin. Predictions of this CK19 gene signature were finally evaluated on 53 human HCCs, upon applying a comparative functional genomics approach [6]. Patients with this signature were enriched in the previously described progenitor-type hepatoblast HCC [6] and had significantly worse prognosis on a univariate analysis.

This work complements previous genomic studies that identified a subgroup of HCCs with a supposedly progenitor cell lineage [6,7], and agree with the poor prognostic value conferred by progenitor-derived signatures [8]. Rules of evidence and guidelines for cancer biomarker studies still require further confirmation of the prognostic value of the CK19 signature for its final incorporation in HCC clinical decision-making algorithms [9] (e.g., relation of the signature to standard prognostic variables like vascular invasion or presence of satellites, multivariate analysis, internal and external validation, etc.). These guidelines (i.e., REMARK [9]) provide a useful road-map for evidence-based evaluation of molecular prognostic markers in oncology. Interestingly, genomic studies conducted in other solid tumors also suggest the prognostic impact of signatures generated from a progenitor/stem cell background (Table 1 [5–7,10–13]). Altogether, they prove the existence of prognostic progenitor traits in solid tumors accessible for genomic monitoring. Hypothetically, common biological features contained in these profiles may code for a distinctive epi-

Table 1. Relevant gene signatures with predicted progenitor/stem cell origin and pronostic impact in human cancer.

Cancer	Gene signature	Biological insights
Liver tumors		
HCC	CK19 signature [5]	Up-regulation of AP-1 transcription factor (JUN/FOS pathway)
HCC	EpCAM signature [7]	Activation of Wnt/beta-catenin signaling pathway
HCC	Hepatoblast signature_ClusterA [6]	Enrichment of JUN and FOS pathway activity
Hepatoblastoma	Hepatoblastoma_C2 class [11]	Activation of Wnt/beta-catenin and Myc signaling pathway
Other tumors		
Breast, lung, prostate, medulloblastoma	Invasiveness gene signature [13]	Activation of RAS and NFκB pathway
Multiple tumors	MTTS/PNS signature [12]	Activation of BMI-1 oncogene pathway
Breast, glioma, bladder	Embryonic stem signature [10]	Over-expression of Nanog, Oct4, Sox2, and c-Myc

thelial progenitor/stem cell signature, potentially able to trace a common ancestor of epithelial-derived malignancies.

Assumption of the CSC theory implies that liver cancer eradication will require drugs able to specifically target these cells, a minor subpopulation within tumor bulk. Sorafenib, the sole systemic agent approved for HCC treatment, probably exerts its anti-tumoral properties by targeting cell proliferation and angiogenesis. Due to the predicted low turnover of CSC, the challenge is set to develop agents with a different mechanistic profile (e.g., differentiation induction) and CSC-specific toxicity [14]. Animal models such as the one used by Andersen et al. [5] would be relevant to evaluate their anti-neoplastic performance in progenitor-derived HCC. An ideal animal model, though, should also recapitulate the underlying liver disease present in most HCC patients (i.e., cirrhosis).

Conflict of interests

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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